REMARKS

Claims 1-29 were pending in the subject application. In the present Office Action, the Examiner required restrictions under 35 USC § 121 to one of the following groups:

I) Claims 1-18 and 29, drawn to a recombinant immunotoxin polypeptide (RIP), classified in Class 424, subclass 183.1.

II) Claims 19 and 20, drawn to a nucleic acid encoding a RIP, classified in Class 514, subclass 44.

III) Claims 21-23 and 28, drawn to a method of treating a patient with a RIP *in vivo*, classified in Class 424, subclass 183.1.

IV) Claim 24, drawn to a method of treating a patient's cell population *in vitro* with a RIP, classified in Class 424, subclass 183.1.

V) Claims 25 and 26, drawn to a method of treating a donor cell population *in vitro* with a RIP, classified in Class 424, subclass 183.1.

VI) Claim 27, drawn to a method of treating a patient to be transplanted with a RIP, classified in Class 424, subclass 183.1.

During a telephone conversation between the Examiner and Diane Furman on November 13, 2000, a provisional election was made with traverse, to prosecute the invention of Group I, claims 1-18 and 29. This provisional election is hereby affirmed.

Therefore, claims 19-28 are withdrawn herein without prejudice. Applicants reserve the right to pursue the subject matter of the canceled claims in later filed application(s).

Claims 8, 17 and 18 have been canceled, and new claims 30, 31, 32, 33 and 34 have been added. Therefore, claims 1-7, 9-16 and 29-34 are presented, herein, for consideration.

The Failure To Comply With 37 CFR 1.821-1.825 Is Corrected.

The specification has been amended to comply with the requirements of 37 CFR 1.821 through 1.825. The descriptions for Figures 1 and 15 have been amended and replaced by descriptions which identify the sequences in those Figures by their SEQ. ID. No. The failure to comply with the requirement of 37 CFR 1.821 through 1.825, noted by the Examiner in Section 7 of the November 21, 2000 Office Action, is believed to be corrected by this addition.

The Rejection Under 35 USC 112 (First Paragraph) Should Be Withdrawn.

Claims 4, 8, 17 and 18 stand rejected under 35 USC 112 (first paragraph) because the Examiner contents that the specification, while being enabling for a RIP comprising a single chain Fv UCHT-1-PE38 (UCHT-1:antiCD3ε antibody; PE38:*Pseudomonas* exotoxin A 38 kD immunotoxin) fusion protein, does not reasonably provide enablement for:

A) A RIP...which binds an epitope formed by the ε and Y chains of human CD3;

B) A RIP...comprising an antibody having a variable region which is at least 80% identical to the variable region of UCHT-1;

C) A RIP...having residues 2-601 or 3-601 of SEQ. ID. NO. 1 and polypeptides which are at least 80% identical thereto.

The Examiner contends that the specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly as it is claimed without an undue amount of experimentation. The Examiner further contends that the scope of the claims are not commensurate with the enablement provided by the disclosure with regard to the breadth of the compositions encompassed by the claims.

The Examiner further contends that, regarding "A" above, (which relates only to claim 4),

The specification discloses a single functional construct, said construct comprising the UCHT-1 antibody. The Examiner contends that this antibody is known to bind only the CD3ε chain and cites to the Pharmingen Technical Data Sheet, 2000.

The Examiner also contends that the specification discloses two additional anti-CD3 antibodies, SP34, which the specification describes as being anti-CD3ε chain only and BC-3, which is also anti-CD3ε chain.

The Applicants respectfully disagree. The recombinant immunotoxin polypeptide claimed in claim 4 is comprised of the UCHT-1 antibody which is a monoclonal mouse anti-human anti-CD3 antibody having an IgG1, Kappa isotype. The UCHT-1 antibody recognizes an epitope contributed by both the ε and Y chains. This is plainly stated in the specification on page 20, line 19 through page 21, line 8. In addition, as discussed in the same portion of the specification, the BC-3 antibody also recognizes an epitope contributed by both the ε and the Y chains.

The Applicants respectfully disagree with the Examiner's contention that the Pharmingen Technical Data Sheet, 2000 states that the UCHT-1 antibody does not bind to the Y chain of CD3. That document only states that UCHT-1 does bind to the ε chain of the CD3/T-cell antigen receptor complex. Likewise, the article cited by the Examiner, i.e., Anasetti et al. (1992), page 845, column 2, only states that "Specificity for the CD3-ε subunit was documented," but the article does not state that antibody BC3 does not bind to the Y chain of CD3.

Therefore the Applicants respectfully suggest that the Examiner has not provided evidence to support the contention that UCHT-1 and BC3 do not bind both the ε and the Y chains of CD3 as plainly stated by the specification, as discussed above.

Therefore, the Applicants respectfully request that the Examiner's rejection, as regards claim 4, be withdrawn.

Claims 8, 17, and 18 also stand rejected. With regard to claims 8, 17 and 18, the Examiner contends that; regarding B and C, discussed above, the specification provides no guidance as to which amino acids may be changed or deleted while antibody ligand-binding activity is retained, just one anti-CD3 antibody is disclosed (UCHT-1) absent any substitutions or deletions and that

given the open percent homology claim language, the total number of claimed antibodies is essentially unlimited, according to the Examiner.

The Examiner contends that, given the lack of guidance, extended experimentation would be required to determine which substitutions would be acceptable to retain ligand-binding activity, and the fact that the relationships between the sequence of a protein and its tertiary structure (i.e., its binding activity) are not well-understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Mertz et al. (ed.); Birkhauser, Boston, MA, pp. 433 and 492-495), it would require an undue amount of experimentation for one of skill in the art to select substitutions to the UCHT-1 antibody structure that retain ligand-binding activity.

In addition, Claims 8, 17 and 18 stand rejected under 35 USC 112 (first paragraph) because the Examiner contends, that these claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The Examiner contends that there is insufficient written description to show that Applicants were in possession of an antibody having a variable region which is at least 80% identical to the variable region of UCHT-1 and that no such variants of the UCHT-1 antibody are disclosed in the specification and that given the essentially unlimited number of antibodies encompassed by the claims, the examiner believes that one of skill in the art would conclude that the specification fails to disclose a representative number of species to describe the claimed genus.

Applicants have canceled claims 8, 17 and 18 and therefore respectfully request that the Examiner withdraw the objections to these claims. However it should be noted that new claims 30, 31, 32, 33 and 34 have been added. No new matter is added by the addition of these claims. These new claims are supported by the specification, in general and especially at pages 14-40 and especially with regard to hybridization conditions at pages 38, line16 through page 39, line 9.

The Rejection Under 35 USC 112 (Second Paragraph) Should Be Withdrawn

Claims 13 and 16 stand rejected under 35 USC 112 (second paragraph). The Examiner contends that these claims are indefinite for failing to particularly point out and distinctly claim the

subject matter, which Applicants regard as the invention. Specifically, the Examiner contends that the laboratory designation "PE38" renders the claim ambiguous and indefinite.

The Applicants respectfully disagree.

The term "PE38" is defined precisely in the specification on page 25, lines 1-13, i.e., PE38 is a 38 KDA fragment of PE, also essentially lacking Domain Ia of the mature PE protein (e.g., lacking amino acids 1-250 of SEQ. ID. No. 3), and also lacking amino acids residues 365 to 380 of SEQ. ID. No. 3, and thus having the amino acid sequence comprising residues 251 to 364 joined to 381 to 613 of SEQ. ID. No. 3.

Therefore, the use of the term PE38 in claims 13 and 16 refers to a precisely defined term in the specification and, therefore, does not render these claims indefinite under 35 USC 112 (second paragraph), and the Examiner is respectfully requested to withdraw the rejection to these claims.

The Rejections Under 35 USC §103(a) Should Be Withdrawn.

Claims 1-18 and 29 stand rejected under 35 USC § 103(a). The examiner contends that these claims are unpatentable over U.S. Patent No. 6,103,235 (2000) in view of Thompson et al. (1995) and Kreitman et al. (1995) or U.S. Patent No. 5,489,525 (1996).

The Examiner contends that the '235 patent teaches a RIP comprising a single chain Fv (which is an F_{ab} fragment) UCHT-1 CD3ε binding domain and a diphtheria toxin (DT) (an ADP-ribosylating exotoxin) and that the reference further discloses a RIP pharmaceutical composition comprising a single chain Fv fused to the carboxy terminus of the exotoxin in a V_L - L - V_H - C - exotoxin conformation.

The Examiner admits that the reference '235 patent teachings differ form the claimed invention in that they do not teach the use of PE38 as the ADP-ribosylating exotoxin in the RIP construct.

The Examiner contends that Thompson et al. teaches that DT immunotoxins are problematic in human treatment protocols because of the potential anti-DT antibody titer already present in most

people previously immunized to DT and that the reference further teaches that one way to overcome this problem would be to use PE immunotoxins.

The Examiner further contends that Kreitman et al. and the '525 patent teach immunotoxic antibody - PE38 fusion proteins.

The Examiner then concludes, that from the combination of the teachings of the references, it would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to produce a RIP, as taught by the '235 patent substituting the PE38 exotoxin for the DT exotoxin, as taught by Kreitman et al. or the '525 patent and that one of ordinary skill in the art would have been motivated to make said substitution because PE exotoxin might be superior to a DT exotoxin given that most humans have pre-existing antibodies to DT (due to prior immunizations) which might interfere with its immunotoxic activity, as taught by Thompson et al.

The Applicants respectfully disagree. Applicants respectfully assert that the cited references do not render the claimed invention obvious, either individually or in combination and traverse the rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success in the combination. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). *See* MPEP §2143 (emphasis added).

The Examiner does not identify support in the references themselves to establish a *prima facie* case of obviousness, but nonetheless, asserts that one skilled in the art would have been motivated to combine the teachings of all four references with a reasonable expectation of success based on the fact that one would expect that most humans have pre-existing antibodies to DT (due to prior immunization) which might interfere with the immunotoxic activity of DT based immunotoxins.

The Applicants contend that there is no suggestion or motivation in the art to arrive at the claimed compositions.

Furthermore, one of ordinary skill in the art would not have had a reasonable expectation of success. It is impossible to know *a priori* the efficacy of a specific fusion immunotoxin that utilizes an sFv as a binding moiety even if the relative affinity of the parental antibody is known or the toxicity of a chemical immunoconjugate using the parental antibody is known.

Thus, it is not possible to know ahead of time that a particular immunotoxin would be problematic in human treatment protocols because of potential anti-DT antibody titer.
In fact, the Applicants contend that a careful reading of Thompson et al. (1995) demonstrates that this reference actually teaches away from the immunotoxin of the invention.

Thompson et al. does state that "in contrast with ricin and Pseudomonas exotoxin-based immunotoxins, there is a potential problem using UCHT-1-CRM9 or other DT based immunotoxins because most people have been immunized against DT." However, Thompson et al. go on to show that an anti-CO3 single-chain immunotoxin sFv DT 390 made with a truncated DT was only slightly affected by the anti-DT antibodies in human sera and was, in fact, found by experiment to be very effective.

In the "Discussion" section, Thompson et al. list the significant advantage of his immunotoxin sFv-DT 390; i.e., it is only one-third the molecular weight of an immunotoxin using the full UCHT-1 and can therefore penetrate into tissue more readily. The sFv-DT 390 could bypass the anti-DT antibodies in *in vivo* situations, and since the sFv-DT 390 contains only the variable region of UCHT-1, it should have less immunogenecity in human anti-mouse antibody responses than native antibody UCHT-1; and finally, the production cost of sFv-DT 390 should be much lower than an immunotoxin based on the full UCHT-1 antibody.

Thus, Thompson et al. teaches that the problems associated with a DT based immunotoxin can be effectively and advantageously dealt with by the methods of his invention, and so teaches away from the use of the completely differently *Pseudomonas* based immunotoxin of the present invention. Nowhere in Thompson et al. is it suggested that the potential problems with DT based immunotoxins are better dealt with by use of a *Pseudomonas* based exotoxin.

Likewise, nowhere in Neville et al. (U.S. Patent 6,103,235) is there any suggestion that *Pseudomonas* toxin should be used instead of the DT disclosed or that patent. In fact, this document does not even mention the possibility of using *Pseudomonas* based toxins in the background of the invention.

Likewise, the disclosure of Kreitman et al. is directly solely to the use of IL2R recombinant toxins targeting IL2Rs to target hematologic malignancies. Nowhere, in Kreitman et al. is there any disclosure or suggestion to use CD3 targeting moiety to target *Pseudomonas* based toxins, or indeed, any other kind of toxins.

In a similar manner, Pastan (U.S. Patent 5,489,525) is directed solely to the use of monoclonal antibodies and binding fragments to target toxins, including; *Pseudomonas* exotoxin A, a drug or a radioisotope, to a human prostate cell for the treatment of prostate cancer. The '525 patent contains no disclosure or suggestion of the use of anti-CD3 antibodies to target a *Pseudomonas* based toxin as in the present invention.

Thus, the Applicants contend that, the Thompson et al. reference actually teaches away from the present invention and that nothing in Kreitman et al. (1995) or U.S. Patent 5,489,525 or Patent 6,103,235 provide any suggestion or motivation to produce the recombinant immunotoxins of the present invention or provide one of skill in the art with any reasonable expectation of success in doing so.

The Applicants, therefore, respectfully suggest that no *prima facie* case of obviousness can be based on these references, alone or in combination, and therefore the Applicants request reconsideration and withdrawal of the rejection under 35 USC 103(a).

CONCLUSION

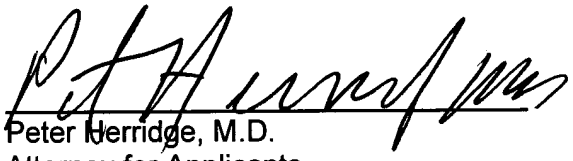
Applicants respectfully request that the remarks of the present response be made of record in the instant application. The provisional election has been confirmed, Figures 1 and 15 have been corrected, and claims 8, 17 and 18 have been canceled. Applicants believe that claims 4, 13 and 16 and new claims 30, 31, 32, 33 and 34 fully meet all statutory requirements for

patentability and that the claims are not rendered obvious within the meaning of 35 USC 103 by any of the cited references alone or in combination.

No new matter is believed to be added by any of the preceding amendments. Thus, consideration and allowance of the pending application are respectfully requested. The Examiner is invited to contact the undersigned counsel by telephone if such contact would expedite prosecution.

Please charge Deposit Account No. 19-0134 in the name of Novartis Corporation in the amount of $390.00 for payment of the extension fee. This amount is believed to be correct for a two-month extension. An additional copy of this paper is hereby enclosed. However, the Commissioner is hereby authorized to charge any additional fees under CFG §1.17 which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis Corporation.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

On page 7 under "Brief Description of the Figures," the description of Figure 1 has been amended as follows:

FIG.1 Schematic diagram showing domain organization of scFv (UCHT-1)-PE38 molecule (SEQ. ID. No.1), prepared in Example 1, consisting of an N-terminal light chain variable region (V_L) of 109 residues, a peptide linker (L) of 16 residues, a heavy chain variable region (V_H) of 122 amino acids, a connector segment (C) of 5 amino acids (KASGG) (SEQ. ID. No. 9), and the PE38 mutant, comprising 347 amino acids ("Toxin").

On page 12, the description of Figure 15 has been amended as follows:

FIG.15 Nucleotide (SEQ. ID. No. 2), and amino acid sequence (SEQ. ID. No. 1), of scFv (UCHT-1)-PE38. DNA sequence encoding the NcoI, HindIII, EcoRI, and BamHI/Bg1II restriction sites used for subcloning, are underlined; the flexible linker separating the V_L from the V_H domains is also underlined. Numbers correspond to nucleotides. Single letter codes denote encoded amino acids. The amino-terminal residues Met and Ala are encoded by the NcoI restriction site that was added to facilitate expression from the *E. coli* plasmid pET 15b. The 3' non-coding DNA between the EcoRI site and the Bg1II/BamHI site is carry-over sequence from the polylinker of an intermediate cloning vector (pLitmus 38, New England Biolabs).